REMARKS/ARGUMENTS

Applicants acknowledge with appreciation the time and courtesies extended by the examiner toward Applicants' representatives during recent telephone interviews. The examiner's insights and comments have advanced the prosecution of the case.

During these interviews, the examiner clarified the outstanding issues and suggested ways of moving the prosecution forward. To this end, Applicants' representative submits a Declaration of Paula McKenna Under 37 C.F.R. §1.132 to address the outstanding issues.

Applicants address the examiner's remarks in the order presented in the Office Action (dated March 26, 2003). All claim amendments are made without prejudice and do not represent an acquiescence in any ground of rejection.

STATUS OF THE CLAIMS

Claims 1-34 are pending. Claims 10-20 are canceled. Claim 1 is amended. Therefore, claims 1-9 and 21-34 are pending after entry of this amendment.

Support for the amendment to claim 1 can be found in claim 1 as originally filed. This amendment is supported by the specification as filed and no new matter has been added.

Claims 1-9 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking written description.

Claims 1-8, 21-28 and 30-34 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hertogs *et al.* (*Antiviral Agents and Chemotherapy*, 1998, IDS paper no. 3) in view of any one of Zazzi *et al.* (*Molecular Biotechnology*, 1998, Paper No. 3), Kozal *et al.* (U.S.Pat No. 5,856,086), Birk *et al.* (*Aids*, 1998), Cabana *et al.* (*Journal of Medical Virology*, 1999) or Boden *et al.* (*JAMA*, 1999).

Claims 1, 9, 21 and 29 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Hertogs *et al.* (*Antiviral Agents and Chemotherapy*, 1998, IDS Paper No. 3) in view of Demeter *et al.* (*Journal of Virological Methods*, 1998, IDS Paper No. 3).

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-9 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. It is submitted that this rejection has been overcome by amendment. More specifically, Applicants have amended claim 1, and in particular, changing "SEQ ID

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No: 1 **or** SEQ ID No: 2" to "SEQ ID No: 1 **and** SEQ ID No: 2" as originally filed (and as fully described in WO97/27480). Therefore, it is respectfully requested that the rejection of claims 1-9 under 35 U.S.C. §112, first paragraph, be removed.

REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-8, 21-28 and 30-34 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Hertogs *et al.* (*Antiviral Agents and Chemotherapy*, 1998, IDS paper no. 3) in view of any one of Zazzi *et al.* (*Molecular Biotechnology*, 1998, Paper No. 3), Kozal *et al.* (U.S.Pat No. 5,856,086), Birk *et al.* (*Aids*, 1998), Cabana *et al.* (*Journal of Medical Virology*, 1999) or Boden *et al.* (*JAMA*, 1999).

The examiner stated that although the specific sequences of SEQ ID NO: 3-21 have not been disclosed in the prior art for the same purpose as disclosed by Applicants, the examiner stated that the sequences that are disclosed in the cited references are functional equivalents of the instant sequences. The examiner cited MPEP 2144.06 for supporting the proposition that in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents (citing *In re* Ruff).

The examiner also stated that the equivalence is related to the end product which is the determination of mutations in the *pol* gene (set out in the preamble of the claim), and noted that although the cited references do not teach the specific primers disclosed in SEQ ID NO: 3-12, the she is of the opinion that one having ordinary skill in the art would have already been directed to the 2.2 kb product from the outer primers disclosed by Hertogs *et al.* and Zazzi *et al.* (who, according to the examiner, indicate that sequencing of this region is necessary for the determination of mutation in the *pol* region). In addition, the other cited references provide ample primers that detect smaller regions within the 2.2 kb product, all of which would produce the equivalent result of sequencing the regions associated with high mutation rates.

As explained in the MPEP, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the

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art, to modify the references or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in Applicants disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Regarding obviousness, Applicants respectfully note that the MPEP §2142 states:

> The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. *If the examiner does not produce a prima facie case, the applicant is under no obligation to submit evidence of nonobviousness.* ...The initial burden is on the examiner to provide some suggestion of the desirability of doing what the inventor has done. "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must *expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning* as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references."

(emphasis added).

As the record indicates, Applicants believe that the cited references cannot support an obviousness rejection. Moreover, Applicants have noted unexpected results when the primers of the instant invention are used. The examiner specifically requested that if Applicants' specific sequences produce an unexpected result, Applicants need to point out what those results are. The MPEP §2141 states:

> Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

Applicants' representative submits a Declaration of Paula McKenna under 37 CFR §1.132 (McKenna Declaration; attached as Exhibit 1), detailing evidence of unexpected results obtained in testing an embodiment of the present invention. As attested to by Dr. McKenna, the primers and methods using these primers, at minimum, produce unexpected results and are therefore distinguishable over the primers and methods in the cited references in view of unexpected results (McKenna Declaration at ¶7).

Dr. McKenna states that in comparing the primers with those of Virco competitors, the Virco primers enable one to detect important mutations associated with drug resistance, in particular mutations at positions 318 and 333 in RT which confer resistance to NNRTIs and NRTIs, respectively. See Harrigan *et al.*, 2002 , *Virol.* 76:6836-6840 (attached as Exhibit B in the McKenna Declaration) and Kemp *et al.* 1998, *J. Virol.* 72:5093-5098 (attached as Exhibit C in the McKenna Declaration). Surprisingly and unexpectedly, these mutations are not detected by others (see McKenna Declaration at ¶11). Dr. McKenna concludes in ¶12 of her declaration that the interpretation of the sequences of viruses tested using Virco primers produces a more accurate and complete resistance profile than other assays not covering that region.

Furthermore, Dr. McKenna stated that the protease is one of the more important proteins for HIV as it cuts the polyproteins into separate functional entities (*e.g.*, the POL gene contains the protease, the reverse transcriptase and the integrase gene). As a result of antiretroviral therapy, mutations are selected that allow the virus to escape drug action. However, these mutations can cause structural alterations in the active site of the protease. It has been found that as a result, compensatory mutations at the protease cleavage sites themselves are in turn increasing in frequency during antiretroviral therapy, causing a further increase in drug resistance (McKenna Declaration at ¶13). The Food and Drug Administration (FDA) has shown an increased interest in the effect of these primary protease mutations (in the functional cavities of the enzymes to overcome antiretroviral therapy (ART)) resulting in secondary compensatory mutations (mutations in, *e.g.*, cleavage sites to overcome structural alterations in the active site of the protease) (McKenna Declaration at ¶14).

The Virco assay and primers unexpectedly cover this FDA interest as the Virco amplicon includes a short partial GAG sequence containing two important cleavage sites for the HIV protease called "p7/p1" and "p1/p6". In this way Virco could to monitor the evolution of the secondary mutations in the downstream part of GAG resulting from PI treatment (McKenna Declaration at ¶14).

Dr. McKenna concluded that, taken together, the foregoing primer characteristics establish that the Virco primers for amplicon generation and sequencing show unexpected results (McKenna Declaration at ¶14). Therefore, as attested to by Dr. McKenna, "As

evidenced by the unexpected results of the Virco primers, I believe that the Virco primers of the present invention would not be obvious to one skilled in the art, such as myself, when looking at the references as cited in Paper No. 21." (McKenna Declaration at ¶14).

Thus, Applicants respectfully suggest that the independent claims are allowable over the cited references. The dependent claims depend from and further limit their respective independent claims, and therefore are allowable as well. For at least these reasons, the Virco primers provide unexpected results. Therefore it is respectfully requested that the rejection of claims 1-8, 21-28 and 30-34 under 35 U.S.C. §103(a) as being unpatentable over Hertogs *et al.* (*Antiviral Agents and Chemotherapy*, 1998, IDS paper no. 3) in view of any one of Zazzi *et al.* (*Molecular Biotechnology*, 1998, Paper No. 3), Kozal *et al.* (U.S. Pat No. 5,856,086), Birk *et al.* (*Aids*, 1998), Cabana *et al.* (*Journal of Medical Virology*, 1999) or Boden *et al.* (*JAMA*, 1999) be withdrawn.

Claims 1, 9, 21 and 29 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hertogs *et al.* (*Antiviral Agents and Chemotherapy*, 1998, IDS Paper No. 3) in view of Demeter *et al.* (*Journal of Virological Methods*, 1998, IDS Paper No. 3).

As stated above, the examiner is of the opinion that the Hertogs reference provides some guidance as to where in the sequence most sequence substitution correlating to a drug resistant phenotype occur. The examiner stated that the ordinary artisan is therefore provided with the necessary guidance in choosing which sequence stretches are important to determine drug resistance and to focus sequences on those regions only. The examiner stated that although the specific sequences of SEQ ID NO: 3-21 have not been disclosed in the prior art for the same purpose, the sequences that are disclosed in the prior art are functional equivalents of the instant sequences.

The examiner cited MPEP 2144.06 for supporting the proposition that in order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on Applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents (citing *In re* Ruff).

The examiner also stated that the equivalence is related to the end product which is the determination of mutations in the *pol* gene (set out in the preamble of the claim), and noted that although the cited references do not teach the specific primers disclosed in SEQ ID NO: 3-12, the she is of the opinion that one having ordinary skill in the art would have

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already been directed to the 2.2 kb product from the outer primers disclosed by disclosed by Hertogs *et al.* and Demeter *et al.* indicate that sequencing of this region is necessary for the determination of mutation in the *pol* region. The examiner further stated that Demeter *et al.* teaches using PCR to determine mutations in the HIV *pol* region and directly sequencing the primary PCR products (citing the sequencing methods in Demeter *et al.*). The examiner states that the reference teaches numerous primers that may be utilized for the original PCR step and the subsequent sequencing step.

Applicants' arguments as applied to the 35 U.S.C. §103(a) rejection of claims 1-8, 21-28 and 30-34 above can be applied here.

Applicants' representative submits a Declaration of Paula McKenna under 37 CFR §1.132 (McKenna Declaration). As attested to by Dr. McKenna, the primers and methods using these primers, at minimum, produce unexpected results and are therefore distinguishable over the primers and methods in the cited references in view of unexpected results (McKenna Declaration at ¶7).

Dr. McKenna states that in comparing the primers with those of Virco competitors, the Virco primers enable one to detect important mutations associated with drug resistance, in particular mutations at positions 318 and 333 in RT which confer resistance to NNRTIs and NRTIs, respectively. See Harrigan *et al.*, 2002 , *Virol.* 76:6836-6840 (attached as Exhibit B in the McKenna Declaration) and Kemp *et al.* 1998, *J. Virol.* 72:5093-5098 (attached as Exhibit C in the McKenna Declaration). Surprisingly and unexpectedly, these mutations are not detected by others (see McKenna Declaration at ¶11). Dr. McKenna concludes in ¶12 of her declaration that the interpretation of the sequences of viruses tested using Virco primers produces a more accurate and complete resistance profile than other assays not covering that region.

Furthermore, Dr. McKenna stated that the protease is one of the more important proteins for HIV as it cuts the polyproteins into separate functional entities (*e.g.*, the POL gene contains the protease, the reverse transcriptase and the integrase gene). As a result of antiretroviral therapy, mutations are selected that allow the virus to escape drug action. However, these mutations can cause structural alterations in the active site of the protease. It has been found that as a result, compensatory mutations at the protease cleavage sites themselves are in turn increasing in frequency during antiretroviral therapy, causing a further

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increase in drug resistance (McKenna Declaration at ¶13). The Food and Drug Administration (FDA) has shown an increased interest in the effect of these primary protease mutations (in the functional cavities of the enzymes to overcome antiretroviral therapy (ART)) resulting in secondary compensatory mutations (mutations in, *e.g.*, cleavage sites to overcome structural alterations in the active site of the protease) (McKenna Declaration at ¶14).

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Dr. McKenna concludes that, taken together, the foregoing primer characteristics establish that the Virco primers for amplicon generation and sequencing show unexpected results (McKenna Declaration at ¶14). Therefore, as attested to by Dr. McKenna, "As evidenced by the unexpected results of the Virco primers, I believe that the Virco primers of the present invention would not be obvious to one skilled in the art, such as myself, when looking at the references as cited in Paper No. 21." (McKenna Declaration at ¶14).

Thus, Applicants respectfully suggest that the independent claims are allowable over the cited references. The dependent claims depend from and further limit their respective independent claims, and therefore are allowable as well. For at least these reasons, the Virco primers provide unexpected results. Therefore it is respectfully requested that the rejection of claims 1, 9, 21 and 29 under 35 U.S.C. §103(a) as being unpatentable over Hertogs *et al.* (*Antiviral Agents and Chemotherapy*, 1998, IDS Paper No. 3) in view of Demeter *et al.* (*Journal of Virological Methods*, 1998, IDS Paper No. 3) be withdrawn.

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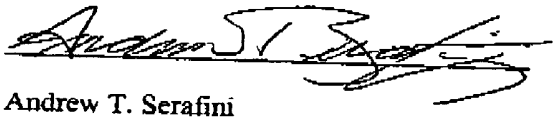
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CONCLUSION

Applicants have enclosed a Transmittal Form with authorization to charge fees in this application to our Deposit Account No. 23-3050. The Commissioner is further authorized to charge any additional fees related to this application and any extension of time to Deposit Account 23-3050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (206) 332-1380.

Date: May 24, 2004



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